REMARKS

After amendment, claims 1-3, 14-19 and 35-36 remain pending in the present application. Claims 4-13 and 20-34 have been canceled *without prejudice* pursuant to the Examiner's restriction requirement and Applicant's election of invention. New claim 36 has been added to reflect the chemical species elected in response to the restriction requirement. No new matter has been added by way of the present amendment. Applicants have amended claim 1 by changing the term "preventing" to the term "reducing the likelihood of" in order to expedite allowance of the present application. The amendment to claim 1 is supported in the specification at page 12 in the last full paragraph where the term "prevention" is defined. No new matter has been added by way of the present amendment.

Applicants note that any claim or subject matter which has been canceled from the previously pending claims is canceled *without prejudice* and Applicants reserve the right to pursue and prosecute any such subject matter in any one or more divisional applications at Applicants' discretion.

The Examiner has rejected the previously pending claims under 35 U.S.C. §112, first paragraph and §103 for the reasons which are set forth in the October 2009 office action on pages 3 through 8. Applicants have amended the claims to address the Examiner's objections/rejection where appropriate and to expedite the issuance of a notice of allowance in this application. Applicants shall address the Examiner's concerns in the sections which are presented hereinbelow. It is respectfully submitted that the application after amendment, is in condition for allowance and such action is earnestly solicited.

The Rejection of Claims 1-3 and 14-19 Under 35 U.S.C.§112, First Paragraph

The Examiner has rejected previously pending claims 1-3 and 14-19 under 35 U.S.C.§112, First Paragraph as being non-enabled for the reasons which are stated in the

office action on pages 3-6. In essence, although the Examiner agrees that the present claims are enabled for a method of treating cognitive impairment as claimed, the Examiner's view is that the present method as it relates to "preventing cognitive impairment" is non-enabled. Applicants respectfully traverse the Examiner's rejection.

The present invention, as set forth in amended claim1 relates to a method of treating or *reducing the likelihood of* cognitive impairment which occurs as a result of acute or chronic sleep deprivation, comprising administering to a subject or patient an effective amount of an AMPA receptor potentiator. It is respectfully submitted that a review of the original patent application and experiments which are presented in the specification clearly evidences that the claims are enabled.

It is noted that the present specification provides ample disclosure of a large number of AMPA receptor potentiators which may be used in the present invention, and provides a clear indication of how those compounds may be used in a manner consistent with the method which is set forth in claim 1 and the claims dependent on claim1. There is no question that the present specification teaches one of ordinary skill in the art how to make and use the present invention without engaging in *undue* experimentation, the *sine qua non* for establishing enablement under 35 U.S.C. §112, first paragraph.

The examiner states that "the specification, while being enabling for the "treatment of cognitive impairment", does not reasonably provide enablement for "*prevention of* cognitive impairment". We note that the term "prevention" in the specification is synonymous with the term "reducing the likelihood of" (see specification p. 12, last full paragraph) and Applicants have amended the claims to reflect that term. Applicants respectfully submit that the presently claimed invention is enabled. Applicants submit that the specification clearly lays out experimentation that demonstrates the ability of an example of the pharmaceutical class of AMPA receptor modulators to prevent/reduce the likelihood of cognitive impairment due to sleep deprivation in a nonhuman primate. The description of the experimentation can be found

on pp 31 and 32 of the specification in addition to the figure legend for the graph of Figure 1.

In the example presented in the specification and described above, it will be noted that both subjects were tested in a cognitive task under three conditions: 1) baseline, which was without drug before testing, following a normal night's sleep, 2) SD, which was without drug before testing, following a night of complete sleep deprivation, and 3) SD+BCM, which was with drug administration before testing, following a night of complete sleep deprivation. The inventors interpreted those data as showing that "BCM at 0.8 mg/kg (iv) ***completely reversed*** the performance deficit," (emphasis added) as evidenced by the data presented in Table 2 on p32 of the application. Applicants respectfully submit that one skilled in the art would conclude that the deficit in cognitive performance was prevented by administration of the drug, which it clearly was.

Perhaps an appreciation for the difference between 'prevention/reducing the likelihood of' and 'treatment' can be illustrated by the established use of the drug alprazolam to prevent panic attacks. If a person experiences panic attacks when driving on a congested motorway, alprazolam could be used two different ways. In a first instance, for example, the person is driving on the motorway and experiences a panic attack. In response to this severe form of anxiety, they pull over to the side and ingest a liquid dosage form of alprazolam and continue driving after a short respect of 15 minutes to allow the drug to act. In this first case, the experience of panic has been **treated**. Alternatively, in a second instance, prior to starting a journey that requires driving on a crowded motorway, a person subject to panic attacks in this situation takes a tablet of alprazolam and waits one or two hours before beginning the journey. In this instance, the drug is used to **prevent/reduce the likelihood** of a panic attack. A carefully controlled study in humans where induced panic attacks were "blocked" by alprazolam pretreatment is completely analogous (See, for example, Sanderson, et al., "Alprazolam blockade of CO2-provoked panic in patients with panic disorder", *Am. J. Psychiatry*, 1994).

The experiments described by Applicants on pp. 31 and 32 of the specification clearly mirror the second scenario which is described above. In the present specification, there was no impairment until the subjects were put into a situation that required use of those neuronal systems that are impaired by sleep deprivation (e.g. hippocampus). Following sleep deprivation, if the subjects had been first tested in order to determine whether a cognitive deficit existed, followed by administration of drug, then that would be 'treatment', as described in the first example above. In the instance where the agent is given to prevent or reduce the likelihood that a cognitive deficit occurred, the agent is said to have prevented or reduced the likelihood of an occurrence of cognitive deficit. Thus, Applicants respectfully submit that the specification clearly gives guidance for means of testing for the **prevention/reducing the likelihood of cognitive impairment** and for administering compounds consistent with those results as set forth in the described experiments of the present specification. Because Applicants have shown that the compounds do prevent/reduce the likelihood of a cognitive impairment, it is respectfully submitted that the presently claimed invention is enabled.

While it is true, as the Examiner opines, that there is a dearth of prior art that demonstrates that a drug can prevent, or even treat the condition of cognitive impairment following sleep deprivation, the reality is that the present invention does precisely that as evidenced by the experiments set forth in the present specification.

Regarding the examiner's claim that undue, unpredictable experimentation is required to practice the claimed invention in terms of preventing cognitive impairment, Applicants respectfully submit that the Examiner's concerns arise from a misinterpretation of the experiments described on pp 31 and 32 and in Figure 1. Furthermore, the experiments in the specification that describe methods for discovering AMPA receptor modulators using *in vitro* methods and use of [18F]-FDG in PET experiments places the methodology of discovering new compounds on a firm footing, thus enabling practice of the claimed invention. These methods are well-known to those skilled in the art. Moreover, the present specification discloses a huge number of compounds which are AMPA receptor potentiators, all of which are effective in treating

and/or preventing/reducing the likelihood of cognitive impairment as a result of acute or chronic sleep deprivation as claimed. Applicants respectfully submit that the presently claimed invention is enabled.

For the reasons which are presented in great hereinabove, Applicants respectfully submit that the presently claimed invention is in compliance with the requirements of 35 U.S.C. §112, first paragraph.

The Rejection of Claims 1-3 and 14-19 As Being Unpatentable Over Rogers, et al.

The Examiner has rejected previously pending claims 1-3 and 14-19 as being unpatentable under 35 U.S.C.§103(a) over the disclosure of Rogers, et al., US. Patent no. 6,313,115 ("Rogers") for the reasons which are presented in the October office action on pages 7-8. The Examiner cites Rogers for teaching the compound 4-benzofurazan-5-ylcarbonyl)morpholine for use in alleviating impairment of memory or other cognitive functions brought on by a deficiency in the number or strength of excitatory synapses or in the number of AMPA receptors and that the treatment has used in humans and well as domesticated and laboratory animals. The Examiner notes that Rogers does not teach acute or chronic sleep deprivation as a cause of the cognitive impairment and the specified patient populations set forth in claims 16-19 of the present application.

Notwithstanding the acknowledged deficiency of Rogers with respect to teachings associated with the present invention, the Examiner argues that the previously pending claimed invention is obvious over the teachings of Rogers, for the specific reasons which are set forth in the office action in the paragraph bridging pages 7 and 8 of the October office action. Applicants respectfully traverse the Examiner's rejection.

The present invention, as presently claimed, is directed to a method for treating or reducing the likelihood of cognitive impairment as a result of acute or chronic sleep deprivation in a patient or subject in need comprising administering to said patient or subject an effective amount of an AMPA receptor potentiator. Applicants respectfully

submit that the presently pending claims are patentable over Rogers, which fails to disclose or suggest the present invention.

The present invention conceptualizes the discovery that transient cognitive impairment which is caused by acute or chronic sleep deprivation may be modulated through AMPA receptors and by administering an AMPA potentiator one can treat or reduce the likelihood of cognitive impairment associated with sleep deprivation. This was unknown in the art prior to the present application and was clearly not disclosed nor suggested by the cited prior art of Rogers.

Note that the drugs which are disclosed in Rogers were shown to improve cognitive behavior in young, healthy animals. As pointed out in the present application on p.4 (and references cited thereon), distinct networks of brain structures appear to be involved in performance of different tasks. Rogers reported that drugs disclosed in the present application were effective for enhancing the function of networks that were recruited to solve a cognitive task under normal sleep conditions. However, a conclusion from the work of others as discussed on pp 3-5 and summarized at the top of p. 5 is that "... brain regions not specifically involved in task performance during normal conditions, were activated during sleep deprivation". Thus, different brain regions are activated during task performance following sleep deprivation as compared to the same task following normal sleep.

One skilled in the art would not find it obvious that the instant drugs would necessarily function to benefit cognitive performance if different brain regions are activated for performance of the task as described on pp. 31 and 32 of this application. The fact that there are no other patent applications or publications showing the use of AMPA receptor modulators in the presently claimed methods prior to the priority date of the present application supports this proposition and is strong evidence of non-obviousness of the present invention. Moreover, at least three pharmaceutical companies other than the assignee of the present application were known to be investigating the same or similar (AMPA potentiator) compounds prior to the period during which the

present application was filed and one of the inventors (Gary A. Rogers) actually made a potent member of the Ampakine family of drugs (CX546) available to scientists through Sigma-Aldrich Chemical Co. Yet, despite the availability of the compounds used in the present invention and intense research activity in this area prior to the filing of the present application, not a single disclosure has emerged which teaches or credibly suggests that AMPA potentiators may be used to treat or reduce the likelihood of cognitive impairment as a result of acute or chronic sleep deprivation.

Given that Rogers is completely devoid of a teaching which discloses or suggests the present invention, Applicants respectfully request that a rejection based upon 35 U.S.C.§103(a) cannot be credibly made. Applicants respectfully request that the Examiner withdraw her rejection of the present invention as being obvious over Rogers.

For the above reasons, it is respectfully submitted that the claims of the present application are not anticipated by any of the cited references. It is respectfully submitted that the claimed invention is patentable over the cited art.

No fee is due for the presentation of the present amendment/response, inasmuch as a number of claims have been deleted from the present application and a single dependent claim has been added. A petition for an extension of time of one month is enclosed as is the appropriate fee.

Small entity status applies to the present application. Please charge any fee due or credit any overpayment made to Deposit Account No. 04-0838.

Respectfully submitted,

Dated: February 8, 2010

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Certificate of Mailing

I hereby certify that this correspondence is being sent by First Class Mail in an envelope addressed to Commissioner for Patents, Mail Stop Amendment, P.O. Box 1450 Alexandria, VA 22313-1450 on February 9, 2010.

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